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Award Number: DAMD17-03-1-0276

TITLE: Exercise to Counteract Loss of Bone and Muscle during Androgen Deprivation Therapy in Men with Prostate Cancer

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Auroa, CO 80045-0508

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PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

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Exercise to Counteract Loss of Bone and Muscle during Androgen Deprivation Therapy in Men with Prostate Cancer

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**6. AUTHOR(S)**

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Auroa, CO 80045-0508

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**13. SUPPLEMENTARY NOTES**

**14. ABSTRACT**
The original objective was to determine whether a 1-year intensive resistance exercise training (RT) program is more effective than a moderate-intensity walking program in ameliorating the effects on body composition of androgen deprivation therapy (ADT) in men with prostate cancer. It was postulated that: 1) RT will attenuate the declines in bone mineral density (BMD) and fat-free mass (FFM) to a greater extent than walking; and 2) both RT and walking will prevent an increase in fat mass. Primary outcomes are lumbar spine BMD and FFM. Secondary outcomes are: total body and hip BMD; fat mass; markers of bone turnover; serum sex hormones; physical functional performance; quality of life, and risk factors for cardiovascular disease (blood lipids, glucose tolerance, arterial stiffness). Because of the inability to enroll the projected number of participants, the study protocol was modified at the time of the 2006 annual IRB review to focus only on the intensive resistance training intervention.

**15. SUBJECT TERMS**
bone mineral density, osteoporosis, sarcopenia, bone turnover, resistance exercise training

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| U | U | U | UU | 11 | **19b. TELEPHONE NUMBER** *(include area code)* |

## Table of Contents

## INTRODUCTION

The original aim of the study was to determine whether a 1-year intensive resistance exercise training (RT) program is more effective than a moderate-intensity walking program in ameliorating the effects on body composition of androgen deprivation therapy (ADT). It was postulated that, in men on ADT for the treatment of prostate cancer: 1) RT will attenuate the declines in bone mineral density (BMD) and fat-free mass (FFM) to a greater extent than walking; and 2) both RT and walking will prevent an increase in fat mass. It was proposed that a total of 40 men would be enrolled and randomized to either the RT or walking exercise programs. Primary outcomes are lumbar spine BMD and FFM**.** Secondary outcomes are: total body and hip BMD; fat mass; markers of bone turnover, to determine whether changes in BMD are the result of changes in bone resorption and/or formation; serum sex hormones, including testosterone, estradiol, estrone, and sex hormone binding globulin; physical functional performance; and quality of life. Local project support will enable additional assessments of risk factors for cardiovascular disease, including blood lipid profile, oral glucose tolerance, and arterial stiffness. These procedures were not included in the original grant application, but were described in the revised protocol that was approved by the local IRB and the HSRRB. Because of the inability to enroll the projected number of participants, the study protocol was modified at the time of the 2006 annual IRB review to focus only on the intensive resistance training intervention.

## BODY

The tasks in the Statement of Work are as follows:

### Task 1: Preparation to initiate studies; months 1 – 3

- secure local IRB and HSRRB approval for study
- apply for research support from the General Clinical Research Center (GCRC)
- apply for research support from the Clinical Nutrition Research Unit (CNRU)
- prepare data forms
- prepare data base
- train research staff

Final approval of the protocol by the HSRRB was 8 August 2004. Thereafter, final approvals were obtained from the GCRC and CNRU for local project support. Recruiting efforts began in November 2004. The protocol was last approved by the local IRB on 9 July 2008; copies of approved documents were not yet available at the time this report was prepared.

### Task 2: Subject recruitment; months 4-21

- enroll 2-3 subjects per month, total of 40 (20 with the change in study design)
- recruiting lectures at local prostate support group meetings
- meetings with private urology clinic staffs
- interactions with health reporters for local media
- place advertisements on newspaper and radio

Enrollment remains below the projected level. Recruitment activities in the past year have focused on contacting urology and medical oncology clinics, both as a means of conserving resources for carrying out the intervention and because direct referral from health care colleagues in the university system has been the primary source of volunteers.

To date, 133 men have inquired about the study, 39 attended an orientation session, 3 are pending for an orientation, 36 provided informed consent, and 13 were enrolled in the study. Of the 13 enrolled, 9 completed final follow-up evaluations, 1 is currently exercising, and 3 dropped out of the study (time commitment, 1; progression of prostate cancer, 1; unknown, 1). At the time of this report, 1 volunteer in the screening process was on hold for follow-up evaluation of hypertension. Of the 23 men who provided informed consent but were not enrolled in the study: 12 dropped out for unknown or personal reasons (no response, 7; not enough time, 2; concern about blood draws, 1; refused to get follow-up evaluation for hypertension, 1; refused to get a bone scintigraphy, 1) and 11 did not qualify (started medications that influence bone metabolism, 4; unrepaired

hernias, 2; positive bone scan, 1; renal disease, 1; exercising too much, 1; oxygen desaturation during ambulation, 1; unstable medical status, 1).

**Task 3: Implement resistance exercise ~~and walking exercise~~ programs~~;~~ months 5 - 32**

- maintain records of attendance, exercise performance
- routine maintenance of equipment
- track progress of individual participants

This task is progressing, though at a slower rate than projected. Because of the slow recruitment and the approaching end of the award period, the protocol was modified at the 2006 IRB review (see discussion following Task 5).

**Task 4: Data acquisition and management; months 4 – 32**

- schedule all baseline and follow-up testing sessions for all participants
- review all data forms prior to computerization
- enter data into database
- perform routine quality control of database
- track blood samples stored for batch analyses of sex hormones and markers of bone turnover to be performed as participants complete the intervention

This task is progressing as planned, though at a slower rate than projected.

**Task 5: Prepare schedule reports; months 1 to 36**

- prepare required progress reports
- secure annual IRB (and HSRRB, if necessary) renewal of protocol
- file serious adverse event forms as necessary
- prepare abstracts for presentation

Annual IRB approval was obtained on 9 July 2008. No serious adverse events have occurred. Because of the inability to recruit the targeted number of participants, the decision was made at the time of the 2006 IRB continuing review to focus the intervention only on the intensive resistance exercise intervention (i.e., discontinue randomization to the walking exercise group). Although this is not an ideal experimental design, the rationale was that it would be better to increase the sample size in the resistance training group to demonstrate significant increases in bone and muscle mass in response to exercise (if they occur), than to distribute the limited number of subjects across two groups and have little chance of demonstrating differences between the groups in the adaptations to exercise. These updates to the protocol were submitted to Mr. Peter Marshall at Fort Detrick, MD, after they were approved by the local IRB (23 Aug 2006). As indicated in the 2007 progress report, confirmation from Mr. Marshall was received in November 2006 that updates were being processed. All materials related to the protocol amendment (and the intervening local IRB continuing review) were re-submitted to the USAMRMC in November 2007. In January of 2008, the PI received an email message regarding the amendment approval from Julie Wilberding, PhD, who requested additional documentation of local IRB approvals. After submitting those documents, the PI received a notice from Dr. Wilberding on 29 January 2008 that the protocol was up to date on continuing review and that all of the amendments were approved on the DOD end.

Based on the recommendation of Dr. Wilberding, the protocol was further modified in February 2008 to include current standard DOD language; this amendment was approved by the local IRB on 19 Feb 2008. In the past year, the consent form underwent minor changes to update standard language used by the local IRB (approved 18 September 2007) and to update location and contact information for the investigators following the move to their new research facilities (approved 11 December 2007).

**KEY RESEARCH ACCOMPLISHMENTS**

At this stage of the project there are no key accomplishments because the study is ongoing.

## REPORTABLE OUTCOMES

At the stage of the project there are no reportable outcomes because the study is ongoing.

## CONCLUSIONS

Throughout the period of award, we have had difficulty enrolling volunteers in the study. The expectation was that the inclusion of a medical oncologist (Dr. Glode), who enthusiastically agreed to be a co-investigator on the award to facilitate the recruitment of patients, would ensure the success of this aspect of the project. Because this did not occur, the investigators have tried both general advertising mechanisms (e.g., newspaper, radio) and more targeted approaches (e.g., other oncology and urology providers and prostate cancer support groups in the Denver Metropolitan area). Most of our successful referrals have come from a few providers, so we maintain regular communication with them. Because another ongoing project in our lab has had recent success using radio ads (i.e., on stations other than those we tried in the past) to recruit older men for a study of testosterone therapy and exercise training, we plan to try this mechanism one more time. Our hope is that we can enroll a few more participants to try to increase the number of finishers to 12.

We remain committed to determining whether an intensive resistance exercise program can generate increases in BMD and fat-free mass in men undergoing ADT. The importance of determining the effectiveness of exercise to counteract some of the effects of ADT remains high. There have been numerous published reviews in the past 2 years on the devastating effects of ADT on the bone health of men with prostate cancer.[1-18] Recent studies indicate that the rate of decline in BMD increases 5- to 10-fold after the initiation of ADT[19] and that the relative risk of osteoporotic fracture is increased by 30% to 300%.[20-22] In 31 men undergoing ADT who were treated with placebo in a bisphosphonate intervention trial,[23] the lumbar spine T-score decreased from an average of -0.8 to -2.5 after only 3 years; all of the participants were classified as either osteopenic (n=13) or osteoporotic (n=18). In one recent retrospective cohort study, the prevalence of osteoporosis for 390 men with prostate cancer undergoing ADT increased from 35% in hormone-naïve patients to 43%, 49%, 60%, 66%, and 81% after 2, 4, 6, 8, and 10+ years of ADT, respectively.[24] In a recent prospective cohort study, the age-adjusted incidence of fracture was higher in men with prostate cancer (31.6 per 1000 person-years) when compared with those without cancer (22.1 per 1000 person-years), and even higher in men with prostate cancer on ADT (40.2 per 1000 person-years).[25] Although pharmacotherapies that have proven to be effective in preventing fractures in postmenopausal women[26] may also be effective men undergoing ADT,[23,27] such therapies do not ameliorate other consequences of ADT that are likely to increase morbidity and mortality.

When compared with either healthy men or men with prostate cancer who are *not* on ADT, men with prostate cancer on ADT lose more muscle, gain more fat (particularly in the abdominal region), and become more insulin resistant and glucose intolerant.[19,28-31] A recent study of 72 men undergoing intermittent ADT found that lean mass decreased by 2.4±0.4% and fat mass increased by 13.8±2.3% (both $p<0.01$) in only 36 weeks.[32] The prevalence of the metabolic syndrome in men undergoing ADT may be more than 50%.[33] In a retrospective study of men with prostate cancer who did (n=1231) or did not (n=7250) receive ADT, the relative risk of incident type 2 diabetes associated with ADT was 1.36 ($p<0.01$).[34] In men with type 1 diabetes, ADT adversely affected glycemic control, C-reactive protein, fibrinogen, PAI-1, t-PA, and lipid profile.[35] A recent retrospective cohort study found that men with newly diagnosed prostate cancer who were on ADT for at least 1 year had a 20% higher risk of serious cardiovascular morbidity compared with those who did not receive ADT.[36] It appears that even short-term ADT increases risk for cardiovascular disease and diabetes. The time to fatal myocardial infarction was found to be shorter in men who had received 6 mo of ADT plus radiotherapy than in those who received radiotherapy only.[37] A large observational study found that ADT increased the risk for coronary heart disease (16%), myocardial infarction (11%), sudden cardiac death (16%), and diabetes (44%), and that increased risk was apparent with only 1 to 4 months of ADT.[38] Collectively, these observational cohort studies strongly suggest that although ADT may be of benefit for attenuating the progression of prostate cancer, the metabolic consequences of ADT increase risk for physical disability, cardiovascular disease, and diabetes.

Because exercise is the *only* intervention that has the potential to favorably influence *all* of these metabolic consequence of ADT and improve survival and quality of life in men with prostate cancer, conducting exercise intervention studies, such as the one in process, is the first step in providing preliminary evidence for the effectiveness of exercise in this population. Although we will not achieve the projected enrollment and had to modify the protocol as a result of this, we believe the data that will be generated will be important given the paucity of exercise intervention studies in this population and could stimulate larger clinical trials to fully evaluate this issue. Despite the suggestion by Galvao et al that exercise training can prevent or reverse some of the adverse effects of ADT,[39] the evidence to support this remains sparse. In fact, the suggestion was based

largely on a small study by those investigators that evaluated changes in body composition, muscle strength, and BMD in response to 5 months of resistance training in 10 men with prostate cancer undergoing ADT (i.e., same study design as our modified protocol).[40] There were significant improvements in muscle strength and functional performance. Fat-free mass and BMD were maintained, but did not increase. Because the current ongoing study involves 12 months of resistance training, this should enable us to determine whether a longer intervention period can generate even more favorable outcomes.

Another no-cost extension of the award period has been granted. Accordingly, it is our intention to continue recruitment efforts through September 2008 and complete all follow-up evaluations of participants by June 2009. This means that, for any new participants enrolled, the period of intervention may have to be reduced by 2-3 months; data analyses will adjust for the period of intervention.

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**APPENDICES**

Appendix A – IRB continuing review Certificate of Approval

Colorado Multiple Institutional Review Board
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Denver Health Medical Center
Veteran's Administration Medical Center
The Children's Hospital
University of Colorado Health Sciences Center
Colorado Prevention Center

Michael Witten
B179

07/18/2008

To: Wendy Kohrt

From: Colorado Multiple Institutional Review Board

Subject: **COMIRB Protocol 02-958 Continuing Review (CRV006) 1st**

Title: EXERCISE TO COUNTERACT LOSS OF BONE AND MUSCLE DURING ANDROGEN DEPRIVATION THERAPY IN MEN WITH PROSTATE CANCER

Review/Panel: **Full Board / Panel B**

Review Date: 9 July 2008

Review Type/Panel: **Full Board/Panel B**

**Review Comments:**

PROTOCOL / SUMMARY
Study Description:
Androgen deprivation therapy (ADT) is the cornerstone of treatment for advanced prostate cancer, but is now being considered at earlier stages of disease severity because of preliminary evidence for success in slowing disease progression and improving survival. One drawback of the earlier initiation and protracted duration of ADT is the deleterious impact it has on body composition, including a loss of bone and muscle mass and an increase in adiposity. Exercise training is the only therapy that can potentially benefit all of the deleterious changes in body composition that occur in response to ADT. This study will determine whether intensive resistance exercise training (RT), which has been shown to increase bone and muscle mass in older men, is effective in men on ADT.

Vulnerable populations:
This protocol involves the following vulnerable subjects: None.

Data Safety Monitoring Plan:
The DSMP as originally approved:

The data and safety monitoring responsibilities will be carried out by the PI with oversight by Medical Monitor, Carol Zapalowski, MD. During the period of study, she will meet with the PI twice a year, or more frequently if necessary, to review study progress and all adverse events, serious and non-serious. Dr. Zapalowski will review all serious and unexpected adverse events associated with the protocol and provide an unbiased written report of the event within ten calendar days of the initial report. There will be no stopping criteria for the study, either for safety or efficacy reasons. Any adverse events that occur will be handled on a case-by-case basis. Problems related to disease progression or treatment will be handled by the participant's PCP; the study team will rely on the advice of the PCP as to whether the participant can continue in the study. Any serious adverse events that are unexpected and related or possibly related to

the intervention will be reported according to COMIRB guidelines. Adverse events that are both serious and unexpected will be immediately reported by telephone to the Deputy for Regulatory Compliance and Quality.

The DSMP as been re-reviewed by the committee and remains appropriate.

The committee has re-reviewed and approved the protocol/protocol summary.

CONTINUING REVIEW FORM
Status:
This study continues to enroll subjects. There are thirty-six subjects enrolled out of the one hundred approved by COMIRB. There have been eleven screen failures and sixteen withdrawals. The withdrawals included the following reasons: 7 had personal reasons, 2 did not return calls, 2 were unwilling/did not have bone scan, 1 had time constraints, 1 had blood draw concerns, 1 moved, 1 wanted to start antiresorptive medication, and 1 had bone mets. The committee found this to be acceptable.

Note: The committee notes that the study population is primarily Caucasian. They encourage the PI to increase recruitment efforts to enroll a more diverse population.
Risks:
There are no new risks in this study.

Previously Approved Amendments Since Last Continuing Review:
PAM010: An addendum was added to the end of the summary protocol at the request of the Department of Defense, the sponsoring agency.

The committee reviewed the previously approved amendment and found it to be appropriate and adequately incorporated into the protocol summary.

Previously Noted Unanticipated Problems Since Last Continuing Review: None.

Previously Noted External Safety Reports Since Last Continuing Review: None.

DSMP
There is a Medical Monitor for this study, Carol Zapalowski, MD. A Safety Officer Review Meeting was held on August 31, 2007 and June 30, 2008 and reports were provided. Recruitment, adherence, retention, protocol changes and adverse events were discussed. At the last meeting, it was planned to conduct one more general recruiting effort through radio ads. There were no other significant issues. The committee found this to be acceptable.

CONSENT FORM
COMIRB Subject Consent Form, Version 4.3, November 27, 2007

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The Children's Hospital
University of Colorado Health Sciences Center
Colorado Prevention Center

Michael Witten
B179

07/18/2008

The committee reviewed and re-approved the consent form.

Note: The following changes are requested upon the next submission or by the next Continuing Review, whichever comes first:
1) In the section, Invitation for Questions, the following standard language should be added, "While your primary source of information pertaining to participation in this study is the principal investigator Wendy Kohrt, a Research Subject Advocate is also available on the General Clinical Research Center at 720-848-6662 to answer questions relating to participation in this study."

HIPAA COMPLIANCE: The COMIRB committee, acting as the COMIRB Privacy Board, noted the submitted HIPAA Authorization form, and the information in the Application and consent form.

HIPAA B form: Included and appropriate.

CONTINUING REVIEW (CRV006), 1st Review: All information required for continuing review and re-approval of the protocol and consent form was included and found to be satisfactory.

CONTINUING REVIEW FREQUENCY: The committee determined that the continuing review frequency is 12 months. The reason for this frequency is due to the specific experience of the PI and other members of the research team, close monitoring of subjects, and oversight by Safety Officer.

RISKS:
The committee determined that this research involves greater than minimal risk. The risks are minimized by qualified investigators, close monitoring of subjects, appropriate inclusion/exclusion criteria, close monitoring and oversight by Medical Monitor.

BENEFITS:
The potential benefits of this research are generalizable knowledge and therapeutic intent.

RISK / BENEFIT RATIO:
The committee has determined that the potential benefits of the study continue to outweigh the known risks.

COMIRB RECOMMENDATION ON CONTINUING Review (CRV006), 1st Review:

X Approved